CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-532

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-532

Submission Date(s):

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August 5, 2002

N000 (B2)

March 14, 2003

Brand Name

Benicar HCTTM

Generic Name

Olmesartan medoxomil-hydrochlorothiazide

ES-866 and HCTZ

Reviewer

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Team Leader

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OCPB Division

One

ORM division

Cardio-renal

Sponsor

Sankyo Pharma Development

Relevant IND(s)

Formulation; Strength(s):

20/12.5 mg, 40/12.5, 40/25 mg tablets

Indication

Hypertension

1 EXECUTIVE SUMMARY

Benicar HCTTM is a combination of olmesartan medoxomil and hydrochlorothiazide (HCTZ) proposed for the treatment of hypertension. The single drug entities are approved for the treatment of hypertension (BenicarTM in April 2002). BenicarTM (olmesartan medoxomil or CS-866) is the medoxomil ester prodrug of the angiotensin II receptor (AT₁) blocker olmesartan (RNH-6270). Hydrochlorothiazide is a thiazide diuretic.

The effectiveness is based on a randomized, double-blind, placebo-controlled, factorial design study (study 866-318) and eight supportive studies. These studies included 2,757 patients (1,230 patients received olmesartan medoxomil and hydrochlorothiazide). The doses used in the pivotal effectiveness study ranged from 10/12.5 mg to 40/12.5 mg and 10/25 mg to 40/25 mg. However, the sponsor did conduct other effectiveness studies using olmesartan medoxomil doses as low as 2.5 mg and 5 mg combined with HCTZ 12.5 mg or 25 mg. The safety is based on the integrated analysis of nine trials.

The potentially marketable drug strengths of Benicar HCTTM are 20/12.5 mg, 40/12.5 mg, and 40/25 mg tablets, however the sponsor only wants approval of three strengths: 20/12.5 mg, 40/12.5 mg and 40/25 mg. The sponsor conducted three bioequivalence (BE) studies with the combination to-be-marketed product since the monoentities were used in the clinical trials: 20/12.5 mg, 40/12.5 mg tablets. The sponsor is only seeking a biowaiver for the 40/25 mg tablet (based on the 20/12.5 mg and 40/12.5 mg tablet data).

10/1.5 10/1.5

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The to-be-marketed 20/12.5 mg and 40/12.5 mg tablets were bioequivalent to their respective single entities.

Olmesartan (RNH-6270) AUC and

Cmax and HCTZ AUC were within the accepted (80, 1.25) 90 % confidence interval.

A biowaiver is granted for the to-be-marketed 40/25 mg tablet. This decision is based on the reference strengths' (20/12.5 mg and 40/12.5 mg tablets) data. The following support the biowaivers:

- Linear pharmacokinetics over the concentration range,
- Proportionately similar compositions between the 40/12.5 mg and 40/25 mg tablets,
- Comparable dissolution profiles in three media, and
- Bioequivalence of the individual formulations.

The following dissolution method and specification are recommended:

CS-866

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than ___ at 45 minutes

HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than ____ at 15 minutes

1.1 Recommendation

NDA 21-532 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A biowaiver is granted for the 40/25 mg tablet. The following dissolution methods and specifications are recommended:

CS-866

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than ____ at 45 minutes

HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than at 15 minutes

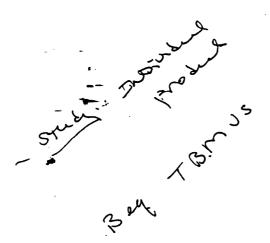
There are no further labeling recommendations.

OCPB briefing held on April 10, 2003. Mehta, Sahajwalla, Ramchandani, Bhattaram and Marroum attended.

B. Nhi Nguyen, Pharm.D. Division of Pharmaceutical Evaluation I Primary reviewer

FT Initialed by Patrick Marroum, Ph.D.

CC: HFD-110 (Fromm, Cooper, Srinivasachar): NDA 21-532; HFD-860 (Mehta, Sahajwalla); CDER central document room



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Abbreviations

Abbreviations				
AUC (0-t)	area under the curve from time zero to time of last quantifiable			
	concentration			
AUC (0)	area under the curve from time zero to infinity			
Cmax	maximum concentration			
CS-866	olmesartan medoxomil			
HCTZ	Hydrochlorothiazide ~			
HPLC	High performance liquid chromatography			
LLOQ	lower limit of quantitation			
NLT	Not less than			
OTC	Over the counter			
RNH-6270	olmesartan (active metabolite of CS-866)			
Tmax	time to Cmax			
T ½	elimination half-life of drug in plasma, calculated as [ln1/ke1]			
k _{el}	elimination rate constant, estimated as [-(slope x 2.303)] from a log linear regression plot of the last 3 to 5 observed plasma concentrations			

	SUMMARY OF CPB FINDINGS
•	The sponsor wants approval of three combination strengths of olmesartan medoxomil/HCTZ 20/12.5 mg, 40/12.5 mg and 40/25 mg tablets), however there are —potentially marketable rug strengths of Benicar HCT TM ; The sponsor conducted — bioequivalence (BE) studies with the combination to-be-marketed product: 20/12.5 mg, 40/12.5 mg and . The sponsor is only seeking a biowaiver for the 40/25 mg tablet (based on the 20/12.5 mg tablet data).
	The to-be-marketed 20/12.5 mg and 40/12.5 mg tablets were bioequivalent to their respective single entities. The mg tablet was not bioequivalent.
	migro officers. The majorate and the control of the
	Olmesartan (RNH-6270) AUC and
	Cmax and HCTZ AUC were within the accepted (80, 1.25) 90 % confidence interval.
	The sponsor demonstrated bioequivalence between HCTZ 12.5 mg capsule and the
	overencapsulated capsule.
	A biowaiver is granted for the to-be-marketed 40/25 mg tablet. This decision is based on the reference strength's (20/12.5 mg and 40/12.5 mg tablets) data. The following support the biowaiver: • Linear pharmacokinetics over the concentration range, • Proportionately similar compositions between the 40/12.5 mg and the 40/25 mg, • Comparable dissolution profiles in three media, and • Bioequivalence to the individual formulations. The sponsor also conducted a study that found the three dosage strengths of CS-866 (10, 20, and 40 mg) to be dose proportional when given as the combination tablet of 10/12.5, 20/12.5 and 40/12.5 mg. HCTZ in the three formulations were bioequivalent.
	In a drug interaction study between olmesartan, HCTZ had no effect on RNH-6270, however the bioavailability of HCTZ in the combination product was 20
	% less than in the single entity.
	The following dissolution method and specification are recommended: CS-866
	Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
	Apparatus: USP II (paddle)
	Speed: 50 rpm Specifications: Q not less than at 45 minutes
	HCTZ
	Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
	Apparatus: USP II (paddle) Speed: 50 rpm
	Specifications: Q not less thantt 15 minutes
	1

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4 QUESTION BASED REVIEW

4.1 General Clinical Pharmacology

· Background

Olmesartan medoxomil (CS-866) is a prodrug that is rapidly and completely hydrolyzed to its active metabolite olmesartan (RNH-6270). RNH-6270 exhibits linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. The absolute bioavailability of RNH-6270 is approximately 26 %. After oral administration, the peak plasma concentration of RNH-6270 is reached in 1 to 2 hours. Food does not affect the bioavailability. RNH-6270 is bound to albumin and α 1-acid glycoprotein, but not to serum globulin. RNH-6270 has a terminal elimination half-life of approximately 13 hours. RNH-6270 is eliminated in urine and feces essentially unchanged. Dose adjustments are not required in mild to moderate renal or hepatic impairment.

The primary basis for effectiveness of CS-866/HCTZ comes from the U.S. study 866-318, a randomized, double-blind, placebo-controlled, parallel-group, factorial design (with and without HCTZ), multicenter study of patients with essential hypertension. Study 866-318 included 502 patients; 247 were randomized to receive olmesartan medoxomil and HCTZ, while 255 were randomized to receive either olmesartan, HCTZ or placebo. This trial had a four week placebo run-in period followed by double-blind treatment in twelve groups for eight weeks. The twelve treatment groups were (mg olmesartan medoxomil/mg HCTZ): 0/0, 10/0, 20/0, 40/0, 0/12.5, 10/12.5, 20/12.5, 40/12.5, 0/25, 10/25, 20/25, and 40/25. The effectiveness is also supported by eight more studies conducted in the US and Europe. In total, 2,757 patients (1,230 patients received olmesartan medoxomil and hydrochlorothiazide)are included in the effectiveness analysis. Olmesartan medoxomil doses as low as 2.5 and 5 mg have been studied. The safety of combination CS-866 and HCTZ is supported by the above mentioned studies, five controlled phase 3 studies submitted with the BenicarTM (olmesartan medoxomil) NDA and the clinical pharmacology studies included in this review. All of the clinical trials used the monoentitities.

4.2 Extrinsic Factors

4.2.1 (Is there a food effect?

There is no food effect with the monoentities. The sponsor did not study the effect of food when taking both drags together. In the pivotal study 866-318, patients were instructed to take their study medication in the morning with breakfast. Since food does not affect the monoentities, it is unlikely that food will affect the combination tablet, thus a study is not warranted.

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General Biopharmaceutics 4.3

Is the market formulation bioequivalent to the formulations used in the clinical 4.3.1 _trials

Yes, the 20/12.5 mg and 40/12.5 mg to-be-marketed tablets are bioequivalent to the single

20/12.5 mg

The ratios for AUC and Cmax are within the 90 % confidence intervals (see tables).

Table 1. _Study 866-126: 20/12.5 mg RNH-6270 Point Estimates and 90 % CI e= 13 m

	AUC (0-t)	AUC (0-oo)	Cmax
C vs. A	1.04 (0.99 – 1.10)	1.04 (0.98 – 1.10)	1.08 (1.02 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.07 (1.01 – 1.13)	1.08 (1.01 – 1.15)

A = 20 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)

B = 20 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)

C = 20 mg CS-866 / 12.5 mg HCTZ tablet

Table 2. Study 866-126: 20/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC (0-t) (ng*h/mL)	3463 ± 799	3603 ± 817	3373 ± 781
AUC (0-0) (ng*h/mL)	3561 ± 843	3695 ± 872	3459 ± 806
Cmax (ng/mL)	560 ± 123	606 ± 137	560 ± 117
Tmax (h)	2.0(1.5-4.0)	2.0 (1.0 – 3.0)	1.5 (1.0 – 4.0)
T ½ (h)	21.4 ± 17.8	20.4 ± 16.3	21.6 ± 13.5
k _{e1}	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02

mean ± SD or median (range)

Study 866-126: 20/12.5 mg HCTZ Point Estimates and 90 % CI Table 3.

	AUC (0-t)	AUC (0-00)	Cmax
C vs. A	1.04 (0.98 – 1.10)	1.05 (0.99 – 1.10)	1.06 (0.98 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.08 (1.02 – 1.14)	1.06 (0.98 – 1.15)

A = 20 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)

B = 20 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)

C = 20 mg CS-866 / 12.5 mg HCTZ tablet

Study 866-126: 20/12.5 mg HCTZ PK parameters Table 4.

Formulation -	A (single entity)	C (combination tablet)	B (single entity)
AUC (0-t) (ng*h/mL)	507 ± 136	522 ± 121	495 ± 138
AUC (0-∞) (ng*h/mL)	566 ± 140	585 ± 118	547 ± 134
Cmax (ng/mL)	90 ± 30	94 ± 32	89 ± 28
Tmax (h)	2.0 (1.0 – 4.0)	1.5 (1.0 –3.0)	1.5 (1.0 – 4.0)
T ½ (h)	11.3 ± 7.2	11.0 ± 2.9	10.6 ± 2.0
k _{e1}	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.01

mean ± SD or median (range)

40/12.5 mg

The ratios for AUC and Cmax are within the 90 % confidence intervals (see tables).

Study 866-138: 40/12.5 mg RNH-6270 Point Estimates and 90 % CI

•	AUC (0-t)	AUC (0-0)	Cmax
C vs. A	0.97(0.90 - 1.04)	0.98 (0.91 – 1.05)	1.03 (0.96 – 1.11)
C vs. B	0.97 (0.91 – 1.05)	0.99 (0.92 – 1.06)	1.03 (0.96 – 1.11)

A = 40 mg CS-866 tablet + 12.5 mg HCTZ capsule (US) B = 40 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)

C = 40 mg CS-866 / 12.5 mg HCTZ tablet

Table 6. Study 866-138: 40/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity) 6601 ± 2056 6743 ± 2091	
AUC (0-1) (ng*h/mL)	6633 ± 1704	6362 ± 2056	6601 ± 2056	
AUC (0) (ng*h/mL)	6759 ± 1699	6569 ± 1526	6743 ± 2091	
Cmax (ng/mL)	1048 ± 289	1071 ± 270	1050 ± 331	
Tmax (h)	2.0	1.5	2.0	
T ½ (h)	19.3 ± 16.0	21.4 ± 21.0	19.0 ± 13.4	

mean ± SD or median (range)

Table 7. Study 866-138: 40/12.5 mg HCTZ Point Estimates and 90 % CI

	AUC (0-t)	AUC (0)	Cmax
C vs. A	0.95 (0.90 - 1.00)	0.96 (0.92 – 1.00)	0.97 (0.90 – 1.04)
C vs. B	0.97 (0.92 – 1.02)	0.96(0.92-1.01)	1.01 (0.93 – 1.08)

A = 40 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)

B = 40 mg CS-366 tablet + 12.5 mg HCTZ tablet (Europe)

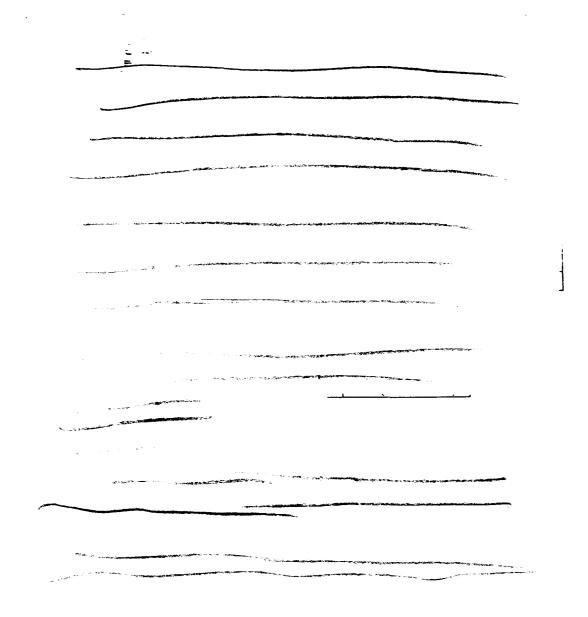
C = 40 mg CS-866 / 12.5 mg HCTZ tablet

Study 866-138: 40/12.5 mg HCTZ PK parameters Table 8.

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC (0-t) (ng*h/mL)	493 ± 100	472 ± 108	489 ± 122
AUC (0) (ng*h/mL)	542 ± 96	522 ± 104	542 ± 121
Cmax (ng/mL)	80 ± 22	78 ± 22	80 ± 30
Tmax (h)	1.75	1.5	1.75
T ½ (h)	9.6 ± 1.8	10.0 ± 1.9	10.2 ± 1.7 _=

mean ± SD or median (range)

).



4.3.1.1 What formulations were used in the trials for Benicar/HCT?

The monoentities were used in all of the clinical trials. Sankyo Co., Ltd in Tokyo, Japan manufactured the 20 mg CS-866 film-coated tablets used in the pivotal study 966-318 and the Phase 3 US study 866-321. Commercially available 12.5 mg MicrozideTM (HCTZ) capsules from ... were used in the pivotal study 866-318 and study 866-321. The 20 mg CS-866 film-coated tablets used in study SE-866CMB/01 conducted by Sankyo Europe GmbH in Germany were manufactured by Sankyo Pharma GmbH of Munich, Germany. The commercially available 12.5 mg HCTZ tablets used in the Sankyo Europe GmbH study were obtained from ... A list of the formulations can be found in the Appendix.

Sankyo Pharma GmbH manufactured the combination product. The formulations of the combination productare listed in the table below.

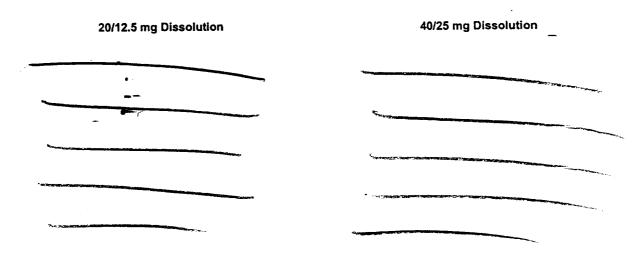
Table 4.3. 1: Quantitative formulation of the Sankyo Pharma GmbH CS-866HCTZ commercial tablets

Ingredient		20/1 2.5 mg tablet	40/12.5 mg tablet	40/25 mg tablet
CS 8661	-	20 กษุ	40 mg	 40 mg
Hydrochlorothiazide 4		12.5 mg	12.5 mg	 25 mg
Microcrystalline cellulose	[-
And the sea of the season of t	L			
Lactose	Γ			
Hydroxypropyl cellulose	-			
Magnesium Stearate	J			
Tablet Core Weight	-			
Coated Tablet Weight	_			
Tablet shape		1 Round	Oval	 Oval
Tablet Core Dimensions		8.5 mm dia.	15 x 7 mm	- 15 x 7 mm

4.3.1.2 Can a waiver be granted for the 40/25 mg tablet? ?

A waiver was requested and can be granted for the 40/25 mg tablet. The data that support this waiver include:

- The 20/12.5 mg to-be-marketed tablet is bioequivalent to the single entities.
- The pharmacokinetics are linear over the dosage range.
- Comparative dissolution profiles are similar in three media. F2 for CS-866 in water and pH 6.8 were 75.4. The F2 for CS-866 in pH 1.2 and for HCTZ were not calculated because of very rapid dissolution. The dissolution profiles are shown below for CS-866.



20/12.5 mg Dissolution

40/25 mg Dissolution



The compositions of the 40/12.5 mg (reference) and the 40/25 mg are proportionally similar. The difference in HCTZ is

Ingredient	40/12.5 mg tablet	40/25 mg tablet	
CS 866 ¹	40 mg	40 mg	
Hydrochlorothiazide	12.5 mg	25 mg	
Microcrystalline cellulose			
	[
Lactose.			
Hydroxypropyl cellulose	[. 		
Magnesium Stearate	<u> </u>		
Tablet Core Weight			
Coated Tablet Weight	1		
Tablet shape	Oval	Oval	
Tablet Core Dimensions	15 x 7 mm	15 x 7 mm	

or Biographic

12 + 12 h

Are the sponsor's recommended dissolution specifications and methodology acceptable?

•	Sponsor's Recommended Dissolution Specifications and Methodology for CS-866
	20/12.5 mg tablet

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

,30m

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than --- at

40/12.5 mg and 40/25 mg tablet

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:____

50 rpm

Specifications:

O not less than -

Sponsor's Recommended Dissolution Specifications and Methodology for HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

O not less than ___at

The sponsor's recommended dissolution specifications and method for olmesartan medoxomil/HCTZ are unacceptable for the following reasons:

- The sponsor's dissolution was corrected for a degradation of ____ Dissolution should be unaltered.
- The sponsor's Q of is too low. A drug product that releases only is less likely to be bioequivalent than a product that releases 100 %. Therefore we are recommending a Q of

The recommended dissolution specifications and method for olmesartan medoxomil/HCTZ are:

CS-866

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than ____ at 45 minutes

HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

5**0** rpm

Specifications:

Onot less than _____, at 15 minutes

5 LABELING

Are the proposed labeling recommendations appropriate?

The labeling for the clinical pharmacology section is composed of the Benicar and hydrochlorothiazide labels. There are no further labeling recommendations.

•		•
,	6	APPENDIX

6.1 Proposed labeling

Draft Labeling Page(s) Withheld

6.2 Individual Study Reviews

6.2.1 Pharmacokinetics - Healthy Volunteers - Bioequivalence

6.2.1.1 866-126: 20 /12.5 mg BE of olmesartan tablets plus HCTZ capsules or HCTZ tablets and olmesartan/HCTZ tablets

Study: 866-126

Volume: 1.35

p. 1 – 3397

Title: A randomized, open-label, three-way crossover bioequivalence study of CS-866 tablets plus hydrochlorothiazide capsules or tablets and CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator:

Study site:

First patient enrolled: August 10, 2001 Last patient completed: August 28, 2001

Objectives: To determine the bioequivalence of the clinical trial supply of CS-866 20 mg tablets and HCTZ 12.5 mg capsules or tablets administered orally in combination versus oral administration of the market image single tablet formulation of CS-866/HCTZ

Study design: randomized, open-label, three-way crossover, single dose study

Duration: approximately 30 days – 88 hours in the clinic on three separate visits, 7 day washout period between visits

Population: Thirty subjects (17 males, 13 females) completed the study, however 36 subjects were planned and only 33 were enrolled.

Table 13. Study 866-126: Demographics of enrolled subjects

I WOLL IN DING	y etc 12 c. = a F
males/females	17/16
Age (yrs)	$26.5 \pm 8 (18 - 44)$
Weight (kg)	$71 \pm 12 (52 - 96)$
Height (cm)	$168 \pm 10 (150 - 185)$
Race n (%)	12 (36 %) Caucasian
	14 (42 %) Black
	† (3 %) Asian
	5 (15 %) Hispanic

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different combinations of CS-866 and HCTZ at each of three different dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose. Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ

concentrations. Urine was also collected and the volume was recorded, however it was not quantified.

Other medications: Except for oral contraceptives, other medications were not allowed during • the study. Any prescription drug was prohibited within 14 days of the dose and any nonprescription drug was prohibited within seven days of the dose.

Treatment: single dose of

- A) 20 mg CS-866 investigational tablet + 12.5 mg HCTZ capsule
- B) 20 mg CS-866 investigational tablet + 12.5 mg HCTZ tablet
- C) 20 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet

Formulation: Sankyo Pharma Development supplied Study drug.

- 20 mg CS-866 investigational tablet batch #B99T20, size
- 12.5 mg HCTZ capsule batch #015103 US commercial supply,
- 12.5 mg HCTZ tablet batch #2145601 European commercial supply.
- 20 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet batch #3139V01004, size

Assay: RNH-6270 was determined in plasma by

Concentrations of HCTZ were method.

determined in plasma using a validated Table 14. Study 866-126: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270		- Commence	·	
			*** Charles and Labor.	
HCTZ	- Andrews Co.	A STATE OF THE PARTY.	distance and the second	
			· white and it is	<i>i</i>

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

Natural-log transformed PK parameters were analyzed by ANOVA. The formulation differences (C vs. A and C vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) bioequivalence criteria.

Results: Both test formulations (A and B) were bioequivalent to the to-be-marketed formulation (C) (see tables).

Table 15. Study 866-126: 20/12.5 mg RNH-6270 Point Estimates and 90 % CI

	AU€ (0-t)	AUC (0)	Cmax
C vs. A	1.04 (0.99 – 1.10)	1.04 (0.98 – 1.10)	1.08 (1.02 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.07 (1.01 – 1.13)	1.08 (1.01 – 1.15)

Table 16. Study 866-126: 20/12.5 mg HCTZ Point Estimates and 90 % CI

	AUC (0-t)	AUC (0)	Cmax
C vs. A	1.04 (0.98 – 1.10)	1.05 (0.99 – 1.10)	1.06 (0.98 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.08 (1.02 – 1.14)	1.06 (0.98 – 1.15)

The plasma concentrations for RNH-6270 and HCTZ are shown in the figures and tables that follow. Generally, RNH-6270 and HCTZ concentrations are higher in the combination tablet, however these differences were insignificant.

Figure 1. Study 866-126: RNH-6270 Cp (mean ±SD)

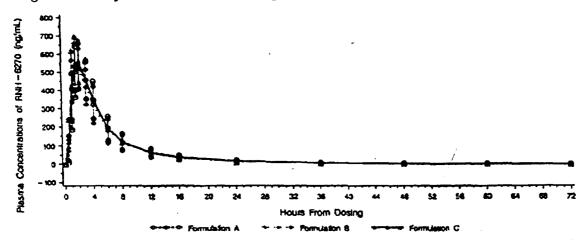
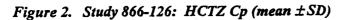


Table 17. Study 866-126: 20/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC (0-t) (ng*h/mL)	3463 ± 799	3603 ± 817	3373 ± 781
AUC (0) (ng*h/mL)	3561 ± 843	3695 ± 872	3459 ± 806
Cmax (ng/mL)	560 ± 123	606 ± 137	560 ± 117
Tmax (h) -	2.0 (1.5 – 4.0)	2.0 (1.0 – 3.0)	1.5(1.0-4.0)
T ½ (h)	21.4 ± 17.8	20.4 ± 16.3	21.6 ± 13.5
k _{e1}	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02

mean ± SD or median (range)



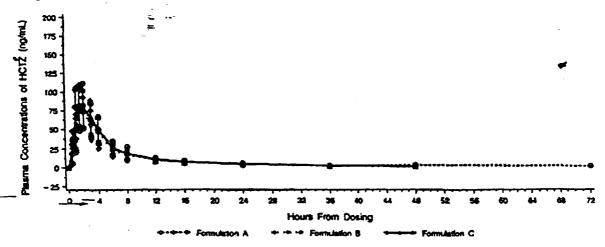


Table 18. Study 866-126: 20/12.5 mg HCTZ PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC (0-4) (ng*h/mL)	507 ± 136	522 ± 121	495 ± 138
AUC (0) (ng*h/mL)	566 ± 140	585 ± 118	547 ± 134
Cmax (ng/mL)	90 ± 30	94 ± 32	89 ± 28
Tmax (h)	2.0(1.0-4.0)	1.5 (1.0 –3.0)	1.5(1.0-4.0)
T ½ (h)	11.3 ± 7.2	11.0 ± 2.9	10.6 ± 2.0
k _{e1}	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.01

mean ± SD or median (range)

Headache, dizziness and nausea were the most commonly reported AEs. One subject withdrew because of nausea and vomiting.

Sponsor's Conclusions: The single drug entities given together as CS-866 20 mg and HCTZ 12.5 mg tablet or 12.5 mg capsule are bioequivalent to the 20/12.5 mg to-be-marketed tablet.

Reviewer's Comments: The tablet batch size of the lot (3139v01004) used for the pivotal BE study was The tablet production size of the 20/12.5 mg tablet is ablets. It is noted that the tablet batch size used in the BE study is less than the recommended of the tablet production size (i.e., the tablet batch size should be at least tablets).

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions.

5.2.1.2 866-139: BE of olmesartan tablets plus HCTZ capsules or HCTZ tablets and olmesartan/HCTZ tablets

Study: 866-139

Volume: 16 - 29 (March 14, 2003) p. 1 - 1821

Title: A randomized, open-label, three-way crossover bioequivalence study of 20 mg CS-866 tablets plus _____, hydrochlorothiazide capsules or tablets and ______ CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator:
Study site:

First patient enrolled: November 16, 2002 Last patient completed: December 6, 2002

Objectives: To determine the bioequivalence of the clinical trial supply of CS-866 20 mg tablets and HCTZ — capsules or tablets administered orally in combination versus oral administration of the market image single tablet formulation of CS-866/HCTZ

Study design: randomized, open-label, three-way crossover, single dose study

Duration: approximately eleven days (264 hours) – 88 hours in the clinic on three separate visits, 7 day washout period between treatment sequences

Population: Thirty-two subjects completed the study. Thirty-six subjects (26 males, 10 females) were enrolled. Unlike the other clinical pharmacology studies, this study contained a higher percentage of Blacks compared to Whites.

Table 19. Study 866-139: Demographics of enrolled subjects

males/females	26 males, 10 females
Age (yrs)	$30 \pm 8 (18 - 45)$
Weight (kg)	$72.3 \pm 10.3 (50.3 - 90)$
Height (cm)	$174.8 \pm 9.5 (152 - 193)$
Race n (%)	5 (14 %) Caucasian
	23 (64 %) Black
	2 (6 %) Asian
	5 (14 %) Hispanic
	1 (3 %) American Indian

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different combinations of CS-866 and HCTZ at each of three different dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose. Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ concentrations.

	mo stady.				
•	A) 20 mg CS-866 invest B) 20 mg CS-866 invest C) 20 mg CS-866/ —	tigational tablet + tigational tablet + -	mg HCTZ tabl	et (European supply)	•
	Formulation: Sankyo F 20 mg CS-866 invest GmbH			y drug. 007, size ————————————————————————————————————	Pharma
- .	 12.5 mg HCTZ caps HCTZ tablet 20 mg CS-866/12.5 size 	- batch #3998V01	008, commercial		01002,
	Assay: RNH-6270 was determined in plasma us Table 20. Study 866-1.	sing a validated	method	concentrations of HCTZ we l.	ere
	Drug Precis	ion Accuracy	Linearity	Sensitivity	
	RNH-6270 HCTZ			Com provide all all all all and all all and all all and all all and all all and all all and all all and all all and all all and all all and all all and all all and all all all and all all all and all all all and all all all all all all all all all al	

Other medications: Except for oral contraceptives, other medications were not allowed during

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

Natural-log transformed PK parameters were analyzed by ANOVA. The treatment differences (C vs. A and C vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the treatment bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) to test bioequivalence.

SAS version 6.12 was used for analysis.

Results: Both test formulations (A and B) were bioequivalent to the to-be-marketed formulation (C) (see tables) for RNH-6270 concentrations. HCTZ total exposure in all treatments was bioequivalent. HCTZ peak exposure was bioequivalent between the market tablet (Treatment C) and the 20 mg CS-866 and HCTZ tablet European clinical supply (Treatment B). However, the point estimate (90 % CI) for the ratio of the peak exposure of

HCTZ between the to-be-marketed tablet and Treatment A (US clinical supply) was 0.85 (0.77, 0.93).

Table 21. Study 866-139: ___ mg RNH-6270 Point Estimates and 90 % CI

·	AUC (0-t)	AUC (0-m)	Cmax
C vs. A	0.99(0.92 - 1.05)	0.98(0.92 - 1.05)	1.01 (0.94 – 1.08)
C vs. B	0.95(0.89 - 1.01)	0.94 (0.88 – 1.00)	0.96 (0.90 – 1.03)

Table 22. Study 866-139: ___ mg HCTZ Point Estimates and 90 % CI

1		AUC (0-t)	AUC (0)	Cmax
	C vs. A	0.91(0.85 - 0.96)	0.92(0.87 - 0.97)	0.85 (0.77 – 0.93)
	C vs. B -	0.94(0.89 - 1.00)	0.95 (0.90 – 1.01)	0.93 (0.85 – 1.02)

The plasma concentrations for RNH-6270 and HCTZ are shown in the figures and tables that follow.

Figure 3. Study 866-139: RNH-6270 Cp (mean ±SD)

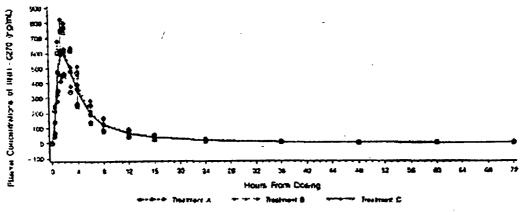
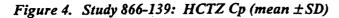
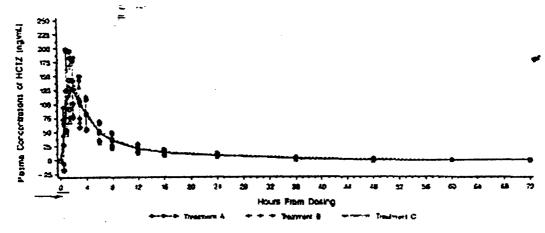


Table 23. Study 866-139: - mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC (0-t) (ng*h/mL)	3716 ± 938	3666 ± 878	3850 ± 923
AUC (0) (ng*h/mL)	3780 ± 957	3727 ± 900	3727 ± 900
Cmax (ng/mL)	632 ± 153	635 ± 137	635 ± 138
Tmax (h)	2.0	1.5	1.5
T ½ (h)	18.6 ± 10.7	18.5 ± 8.9	18.5 ± 8.9

mean ± SD or median





Trailment A = 20 mg CS-886 Tacks + mg HCTZ Cepsure(US);
Trailment B = 20 mg CS-866 Tacks + HCTZ Technique(CTZ Tech

Table 24. Study 866-139: - ng HCTZ PK parameters

Formulation	A/(single entity)	C (combination tablet)	B (single entity)	
AUC (0-t) (ng*h/mL)	1053 ± 308	969 ± 317	1019 ± 308	
AUC (0-∞) (ng*h/mL)	1094 ± 306	1015 ± 314	1061 ± 305	
Cmax (ng/mL)	173 ± 62	148 ± 52	160 ± 61	
Tmax (h)	1.5	1.8	2.0	
T ½ (h)	10.5 ± 1.7	11.3 ± 2.3	10.5 ± 2.4	

mean ± SD or median (range)

Headache was the most commonly reported AEs. No subject withdrew due to an AE.

Sponsor's Conclusions:

- The RNH-6270 in all treatments was bioequivalent.
- HCTZ total exposure in all treatments was bioequivalent.
- HCTZ peak exposure was bioequivalent between the _____ narket tablet (Treatment C) and the 20 mg CS-866 and ____ HCTZ tablet European clinical supply (Treatment B). However, the point estimate (90 % CI) for the ratio of the peak exposure of HCTZ between the to-be-marketed tablet and Treatment A (US clinical supply) was 0.85 (0.77, 0.93). This small decrease in peak exposure is not considered clinically significant.

Reviewer's Comments: The tablet batch size of the lot (3148v01002) used for the pivotal BE study was which is greater than of the production batch size. This is acceptable. The tablet production size of the mg tablet is tablets.

Reviewer's Conclusions:

- The AUC and Cmax of RNH-6270 in the mg to tablet are similar to the single entities.
- The HCTZ AUC in the mg' ____ tablet is similar to that in the single HCTZ tablet.
- The HCTZ Cmax in the to-be-marketed tablet was on average 15 % lower than the single HCTZ US tablet. The 90 % CI for the ratio of the peak exposure of HCTZ between the to-be-marketed tablet and the US clinical supply was (0.77, 0.93). This small decrease in peak exposure is not considered clinically significant.

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6.2.1.3 866-138: 40 /12.5 mg BE of olmesartan tablets plus HCTZ capsules or HCTZ tablets and olmesartan/HCTZ tablets

Study: 866-138

Volume: 1-15 (March 14, 2003)

p. 1 – 1807

Title: A randomized, open-label, three-way crossover bioequivalence study of 40 mg CS-866 tablets plus 12.5 mg hydrochlorothiazide capsules or tablets and 40/12.5 mg CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator:

Study site:

First patient enrolled: December 21, 2002 Last patient completed: January 7, 2003

Objectives: To determine the bioequivalence of the clinical trial supply of CS-866 40 mg tablets and HCTZ 12.5 mg capsules or tablets administered orally in combination versus oral administration of the market image single tablet formulation of CS-866/HCTZ

Study design: randomized, open-label, three-way crossover, single dose study

Duration: approximately eleven days (264 hours) - 88 hours in the clinic on three separate visits, 7 day washout period between treatment sequences

Population: Thirty-eight subjects (26 males, 12 females) completed the study, however 42 (27 males, 15 females) were enrolled.

Table 25. Study 866-138: Demographics of enrolled subjects

males/females	27/15
Age (yrs)	$28.4 \pm 8 (19 - 44)$
Weight (kg)	$74.6 \pm 11.7 (52.3 - 99.1)$
Height (cm)	$175.5 \pm 10.6 (152 - 193)$
Race n (%)	32 (76 %) Caucasian
	3 (7 %) Black
	2 (5 %) Asian
	3 (7 %) Hispanic
	2 (5 %) Other

mean ±SD (range)_

Procedure: Subjects were randomized to receive a single dose of one of three different combinations of CS-866 and HCTZ at each of three different dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose. Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study.

Treatment: single dose of

A) 40 mg CS-866 investigational tablet + 12.5 mg HCTZ capsule - US supply

B) 40 mg CS-866 investigational tablet + 12.5 mg HCTZ tablet - European supply

C) 40 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet ~

Formulation: Sankyo Pharma Development supplied Study drug.

- 40 mg CS-866 investigational tablet batch #B00T18, size manufactured by Sankyo Co., Ltd.
- 12.5 mg HCTZ capsule batch #032658, commercial size.
- 12.5 mg HCTZ tablet batch #2145601, commercial size, -
- 40 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet batch #3140V01019,
 size manufactured by Sankyo Pharma GmbH

Assay: RNH-6270 was determined in plasma by determined in plasma using a validated method.

Table 26. Study 866-138: Assay quality control

بتصين

Drug	Precision	Accuracy ·	Linearity	Sensitivity
RNH-6270			Control of the Contro	
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HCTZ	AND DESCRIPTION OF THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TWO IS NAMED IN COLUMN TWIND TWO IS NAMED IN COLUMN TWO IS NAMED IN COLUMN TWO IS NAMED IN	-	-	
	- Andrews (Barbara)	· Charge and a contract of the	The second secon	

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

Natural-log transformed PK parameters were analyzed by ANOVA. The formulation differences (C vs. A and C vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) bioequivalence criteria.

Results: Both test formulations (A and B) were bioequivalent to the to-be-marketed formulation (C) (see tables).

Table 27. Study 866-138: 40(12.5)mg RNH-6270 Point Estimates and 90 % CI

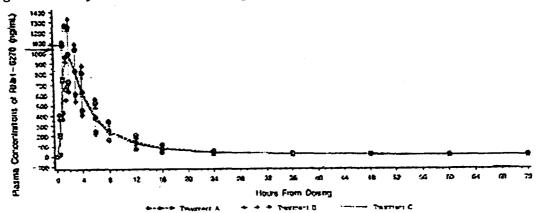
14010 271	AUC (0-t)	AUC (0-w)	Cmax
C vs. A	0.97 (0.90 – 1.04)	0.98(0.91 - 1.05)	1.03 (0.96 – 1.11)
	0.97 (0.91 – 1.05)		

Table 28. Study 866-138: 40/12.5 mg HCTZ Point Estimates and 90 % CI

	AUC (0-t)	AUC (0-m)	Cmax
C vs. A	0.95 (0=90 - 1.00)	0.96 (0.92 – 1.00)	0.97 (0.90 – 1.04)
C vs. B	0.97(0.92 - 1.02)	0.96 (0.92 – 1.01)	1.01 (0.93 – 1.08)

The plasma concentrations for RNH-6270 and HCTZ are shown in the figures and tables that follow.

Figure 5. Study 866-138: RNH-6270 Cp (mean ±SD)



Treasment A 40 mg CS - 286 Table + 125 mg HCTZ CapsuleUS).
Treasment B - 40 mg CS - 286 Table + 125 mg HCTZ Table(Europa);

Treatment C - 40 mg CS - 90612 5 mg HCTZ Commination Tablet.

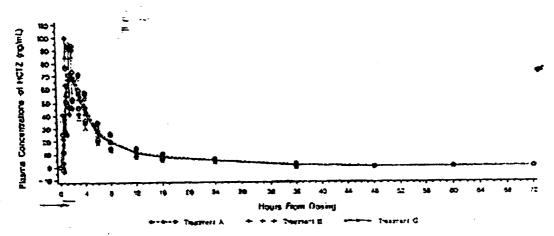
Source Data Table 3.1

Table 29. Study 866-138: 40/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	(single entity) C (combination tablet)	
AUC (0-t) (ng*h/mL)	6633 ± 1704	6362 ± 2056	6601 ± 2056
AUC (0) (ng*h/mL)	6759 ± 1699	6569 ± 1526	6743 ± 2091
Cmax (ng/mL)	1048 ± 289	1071 ± 270	1050 ± 331
Tmax (h)	2.0	1.5	2.0
T ½ (h)	19.3 ± 16.0	21.4 ± 21.0	19.0 ± 13.4

mean ± SD or median (range)

Figure 6. Study 866-138: HCTZ Cp (mean ±SD)



Treatment A = 40 mg CS=266 Tablet + 12.5 mg HCTZ Calcaulations).
Treatment B = 40 mg CS=966 Tablet + 12.5 mg HCTZ Tablet(Europa);
Treatment C = 40 mg CS=86612.5 mg HCTZ Combination Tablet
Source Cable Tablet 3.7

Table 30. Study 866-138: 40/12.5 mg HCTZ PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)	
AUC (0-t) (ng*h/mL)	493 ± 100	472 ± 108	489 ± 122	
AUC (0) (ng*h/mL)	542 ± 96	522 ± 104	542 ± 121	
Cmax (ng/mL)	80 ± 22	78 ± 22	80 ± 30	
Tmax (h)	1.75	1.5	1.75	
T ½ (h)	9.6 ± 1.8	10.0 ± 1.9	10.2 ± 1.7	

mean ± SD or median (range)

Headache and dizziness were the most commonly reported AEs.

Sponsor's Conclusions: The single entities given together as CS-866 40 mg and HCTZ 12.5 mg tablet or 12.5 mg capsule are bioequivalent to the 40/12.5 mg to-be-marketed tablet.

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions.

6.2.1.4 866-134: HCTZ 12.5 mg BE of capsule and overencapsulated capsule

Study: 866-134

Volume: 1.52

p. 1 - 1184

Title: A randomized, open-label, two-way crossover bioequivalence study of hydrochlorothiazide capsules in healthy adult volunteers

Principal investigator:

Study site:

First patient enrolled: December 14, 2001 Last patient completed: December 23, 2001

Objectives: To determine the bioequivalence of HCTZ 12.5 mg following oral administration of two different encapsulated dosage forms

Study design: randomized, open-label, two-way, crossover, single dose study

Duration: approximately 14 days – 64 hours in the clinic on two separate visits, 7 day washout period between visits

Population: Twenty-nine subjects (16 males, 13 females) completed the study, however 30 were enrolled.

Table 31. Study 866-134: Demographics of enrolled subjects

males/females	16/14
Age (yrs)	$24.5 \pm 6 (18 - 44)$
Weight (kg)	70 ± 11 (47 – 89)
Height (cm)	$171 \pm 10 (152 - 188)$
Race n (%)	15 (50 %) Caucasian
	12 (40 %) Black
	3 (10 %) Asian

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of two different HCTZ dose forms at each of two dosing periods. Subjects spent 64 hours in the clinic during each visit for a total of 128 hours during the study. A seven day washout period separated each dose.

Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study. Any prescription drug was prohibited within 14 days of the dose and any nonprescription drug was prohibited within seven days of the dose.

Treatment: single dose of

- A) 12.5 mg HCTZ capsule used in study 866-126
- B) 12.5 mg HCTZ overencapsulated capsule used in study 866-318 phase 3 factorial for blinding purposes

Formulation:

- 12.5 mg HCTZ tcapsule batch #015103 US commercial supply reference.
- 12.5 mg HCTZ overencapsulated (with a capsule batch #1006138/02, size test.

overencapsulated HCTZ capsules by using capsules ________also

Assay: Concentrations of HCTZ were determined in plasma using a validated method.

Table 32. Study 866-134: Assay quality control

THUIC JE. DIM	.y 000 15 71 1	roomy quantity		
Drug	Precision	Accuracy	Linearity	Sensitivity
HCTZ				
			The same of the sa	

Pharmacokinetics: Plasma samples for HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 post dose.

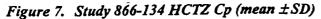
Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

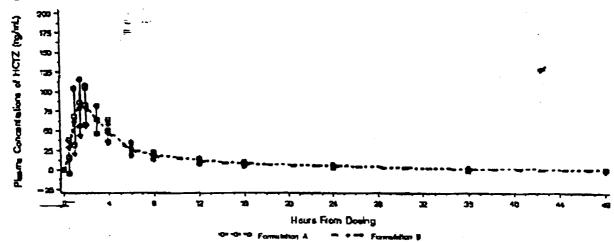
Natural-log transformed PK parameters were analyzed by ANOVA. The formulation differences (A vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) bioequivalence criteria.

Results: The two formulations of HCTZ 12.5 mg capsule are bioequivalent.

Table 33. Study 866-134: HCTZ Point Estimates and 90 % CI

	AUC (0-t)	AUC (0)	Cmax
A vs. B	0.98 (0. 93 – 1.02)	0.98 (0.93 – 1.02)	1.01 (0.94 – 1.08)





Formulation A = 125 mg HCTZ Market—Image Capsule
Formulation B = 125 mg HCTZ Over—Encapsulated Market—Image Capsule

Table 34. Study 866-134: HCTZ PK parameters

Formulation	A (to-be-marketed cap)	B (overencapsulated cap)
AUC (0-t) (ng*h/mL)	550 ± 134	532 ± 108
AUC (0) (ng*h/mL)	604 ± 134	582 ± 102
Cmax (ng/mL)	96 ± 29	96 ± 27
Tmax (h)	1.5 (1.0 – 4.0)	1.5 (1.0 – 4.0)
T ½ (h)	10.1 ± 1.8	10.8 ± 2.9
k _{e1}	0.07 ± 0.01	0.07 ± 0.02

mean ± SD or median (range)

Headache, reported by four subjects was the most frequently reported AE.

Sponsor's Conclusions: The two capsule formulations of HCTZ 12.5 mg are bioequivalent.

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions.

6.2.2 Pharmacokinetics – Healthy volunteers – dose proportionality

6.2.2.1 866-127: Dose proportionality: 20/12.5 and 40/12.5 mg

Study: 866-127

Volume: 1.45

p. 1 - 2050

Title: A randomized, open-label, three-way crossover study of different strength of CS-866 - hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator:
Study site:

First patient enrolled: September 7, 2001 Last patient completed: September 24, 2001

Study design: randomized, open-label, three-way, crossover, single dose study

Duration: approximately 28 days – 88 hours in the clinic on three separate visits, 7 day washout period between visits

Population: Eighteen subjects were enrolled and completed the study.

Table 35. Study 866-127: Demographics.

Tuble 33. Study 000-127. Demographics:		
males/females	9/9	
Age (yrs)	$31.6 \pm 8 (20 - 43)$	
Weight (kg)	$73 \pm 14 (52 - 99)$	
Height (cm)	$172 \pm 10 (152 - 188)$	
Race n (%)	9 (50 %) Caucasian	
	6 (33 %) Black	
	1 (5 %) Asian	
	2 (11 %) Hispanic	

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different CS-866/HCTZ doses at each of three dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose.

Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study. Any prescription drug was prohibited within 14 days of the dose and any nonprescription drug was prohibited within seven days of the dose.

Treatment:	single	dose	of
------------	--------	------	----

- A) CS-866/HCTZ 1
- B) CS-866/HCTZ 20/12.5 mg to-be-marketed capsule
- C) CS-866/HCTZ 40/12.5 mg to-be-marketed capsule

Formulation: Study drug was supplied by

- A) CS-866/HCTZ mg to-be-marketed capsule batch #3138V01006
- B) CS-866/HCTZ 20/12.5 mg to-be-marketed capsule batch #3139V01004
- C) CS-866/HCTZ 40/12.5 mg to-be-marketed capsule batch #3140V01005 /

Assay: RNH-6270 was determined in plasma by — Concentrations of HCTZ were determined in plasma using a validated — method.

Table 36. Study 866-127: Assay quality control

Precision	Accuracy	Linearity	Sensitivity
	1		
-		-	-
		and the same of th	
	Precision	Precision Accuracy	

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose. Urine was collected predose and at the following time intervals post-dose: 0-4, 4-12, 12-24, 24-48 and 48-72 hours postdose, but were only analyzed if necessary.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

RNH-6270 AUCs and Cmax were used to assess dose proportionality using a power model. ANCOVA was performed on the log transformed PK data with subject (random effect), period and dose as factors, and ln(dose) as covariates. Estimates of the proportionality parameter (obtained from the slope estimate for natural log-transformed dose [ln(dose)] with its confidence interval (CI) were used to quantify the degree of non-proportionality. The sponsor declared dose proportionality if all of the 90 % CI for AUCs and Cmax were within the interval (0.68, 1.32).

For HCTZ, the natural-log transformed AUCs and Cmax were analyzed by ANOVA. The formulation differences (A vs. B, A vs. C, and B vs. C) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) to test bioequivalence hypotheses.

Results: The RNH-6270 in the combination tablets were dose proportional. (See table.)

Table 37. Study 866-127: RNH-6270 90 % CI for dose proportionality

AUC (0-t)	AUC (0)	Cmax
0.853 (0.803 – 0.904)	0.853 (0.803 - 0.902)	0.798 (0.749 – 0.847)

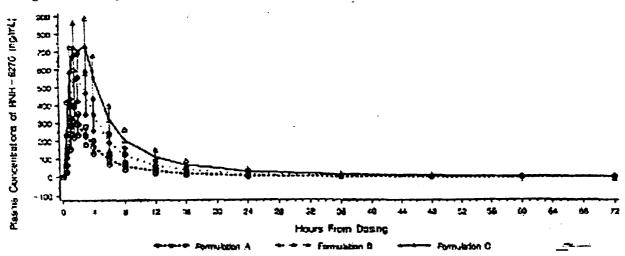
RNH-6270 PK and plasma concentrations are shown in the table and figure below.

Table 38. Study 866-127: RNH-6270 PK parameters

Formulation	A	B (20/12.5 mg)	C (40/12.5 mg)
AUC (0-t) (ng*h/mL)	1841 ± 468	3626 ± 955	5987 ± 1471
AUC (0) (ng*h/mL)	1912 ± 518	3760 ± 1046	6195 ± 1541
Cmax (ng/mL)	318 ± 76	587 ± 126	959 ± 202
Tmax (h)	1.5 (1.5 – 2.0)	2.0 (1.0 – 3.0)	2.0(1.0-3.0)
T ½ (h)	28.7 ± 21.9	25.2 ± 24.1	25.3 ± 16.9
k _{e1}	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02

mean ± SD or median (range)

Figure 8. Study 866-127: RNH-6270 Cp (mean \pm SD)



The HCTZ in the combination tablets were bioequivalent. (See table.)

Table 39. Study 866-127: HCTZ Point Estimates and 90 % CI

	- AUC (0-t)	AUC (0-m)	Cmax
A vs. B	1.01 (0.95 – 1.08)	1.01 (0.95 – 1.07)	1.03 (0.96 – 1.11)
A vs. C	1.05 (0.99 – 1.13)	1.04 (0.90 – 1.10)	1.06 (0.90 – 1.14)
B vs. C	1.04 (0.98 – 1.11)	1.03 (0.97 – 1.09)	1.02 (0.95 – 1.10)

HCTZ PK and plasma concentrations are shown in the table and figure below.

Figure 9. Study 864-127: HCTZ Cp (mean ±SD)

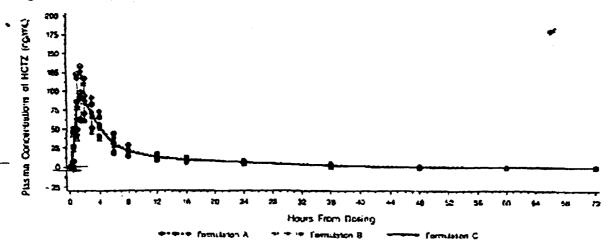


Table 40. Study 866-127 HCTZ PK parameters

Formulation	A -	B (20/12.5 mg)	C (40/12.5 mg)
AUC (0-t) (ng*h/mL)	638 ± 171	630 ± 168	603 ± 151
AUC (0-∞) (ng*h/mL)	679 ± 167	675 ± 166	654 ± 155
Cmax (ng/mL)	105 ± 30	104 ± 35	101 ± 33
Tmax (h)	1.5 (1.0 – 2.0)	1.5 (1.0 –3.0)	1.5 (1.0 – 3.0)
T ½ (h)	10.9 ± 2.0	10.6 ± 2.3	10.6 ± 1.5
K _{el}	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01

mean ± SD or median (range)

Headache was the most common AE reported.

Sponsor's Conclusions: The three dose strengths of CS-866 were dose proportional. HCTZ in the three formulations were bioequivalent.

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions. The wide confidence intervals for RNH-6270 are likely because the study is underpowered.

6.2.3 Drug Interaction

6.2.3.1 SE-866 CMB/01: Interaction study between RNH-6270 and HCTZ using 20 mg of CS-866 and 25 mg of HCTZ tablets

Study: SE-866 CMB/01

Volume: 1.55

p. 1 - 3397

Title: The effect of the combination of the oral angiotensin II antagonist CS-866 and hydrochlorothiazide on pharmacokinetics, safety, and tolerability in healthy male subjects

Principal investigator:

Study site:

First patient enrolled: January 12, 2000 Last patient completed: April 27, 2000

Objectives: Primary - To assess the influence of CS-866 on the PK of HCTZ and the influence of HCTZ on RH-6270 at steady state.

Secondary – Evaluate the PK parameters of RNH-6270 and HCTZ in urine at steady state to assess the safety and tolerability of the different treatments using ECG, BP, pulse rate (abbreviated PR by the sponsor), and laboratory safety tests.

Study design: randomized, open-label, three-way crossover

Duration: 38 days: 7 treatment days (x 3 treatments) plus a 7 day washout period

Population: Twenty-four healthy male subjects were enrolled, however 23 completed the study. One subject withdrew due to an SAE.

Table 41. Study SE-866 CMB/01: Demographics of enrolled subjects

Males	24
Age (yrs)	$32 \pm 6 (21 - 42)$
Weight (kg)	$74 \pm 12 (59 - 94)$
Height (cm)	178 ± 8 (164 – 191)
Race n (%)	24 (100 %) Caucasian

mean ±SD (ranges)

Procedure: Subjects were randomized to receive one of three treatments for seven days. A 7-14 day washout period separated each treatment. Blood and urine were collected for pharmacokinetic assessments on the last dosing day (Day 7) of each treatment period.

Other medications: Other medications, including OTC medications were not allowed for seven days prior to and during the study.

Treatment: One dose was taken daily at 8:00 am (± 1 hour) for seven days following an overnight fast of ~12 hours. The dose was taken with 200 mL of water. On Day 7 of each treatment period, breakfast was served after the 4 hour blood sample, lunch was served seven hours after dosing and another meal was served 11 hours after dosing.

- A) 20 mg CS-866 tablet
- B) 25 mg HCTZ tablet (HCTZ
- C) 20 mg CS-866 tablet + 25 mg HCTZ tablet

Formulation:

- 20 mg CS-866 film-coated tablet batch #2234v99001, manufactured by Sankyo Pharma
 GmbH
- 25 mg-HCTZ tablet (HCTZ- batch #7080275t, manufactured by

Assay: RNH-6270 was determined in plasma by Concentrations of HCTZ were determined in plasma using a validated method.

Table 42. Study se-866 cmb/01: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270				y Committee Co.
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HCTZ			A STATE OF THE PARTY OF THE PAR	gant to the same of the same o
TC12			-	
		-		

Concentrations of RNH-6270 and HCTZ were determined in urine using a validated method.

Table 43. Study se-866 cmb/01: Assay quality control in urine

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270				
			Control of the Contro	
HCTZ	· ·	ALLEGE TO S		-
				•

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last dose on Day 7. Samples were also collected predose on Days 1, 5 and 6 for RNH-6270 (treatments A and C) and HCTZ (treatments B and C).

Urine was collected on Day 7 at the following periods after the last dose: 0-4 h, 4-8 h, 8-12 h, and 12-24 h. Concentrations of HCTZ in urine were determined for Treatments B and C. Concentrations of RNH-6270 in urine were determined for Treatments A and C.

Primary PK parameters were derived from the plasma concentrations. Predose and terminal values below the LOQ were set to zero.

Equivalence of the PK parameters, AUC and Cmax were investigated using the two one-sided test approach by Schuirmann. SAS ver 6.12 was used for the analysis.90 % confidence intervals were constructed.

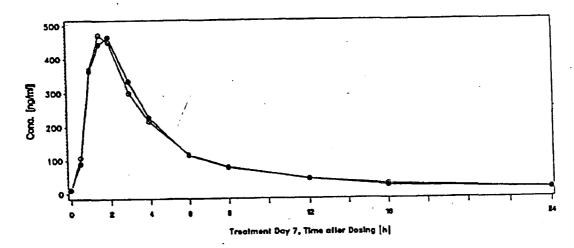
• Results: The RNH-6270 in the two formulations were not bioequivalent. Although the point estimates were near unity, the confidence intervals were outside of the accepted 0.80 -1.25.

Table 44. Study se866cmb/01: RNH-6270 Point Estimates (geometric mean) and 90 % CI

	AUC (ss,t)	Cmax
C vs. A	1.02 (0.67 – 1.55)	1.00 (0.60 – 1.64)

The median plasma concentrations for RNH-6270 are shown in the figure below.

Figure 10. Study se-866 cmb/01: RNH-6270 Cp (median)



Treatment A C

Table 45. Study se866cmb/01: RNH-6270 PK parameters (n=23)

Formulation	A (single)	C (combination)
AUC (ss,t) (ng*h/mL)	1755.1 (96 %)	1790.4 (93 %)
Cmax (ng/mL)	343.2 (128 %)	341.8 (118 %)
Tmax (h)	1.5 (0 -3.0)	1.5(1.0-3.0)

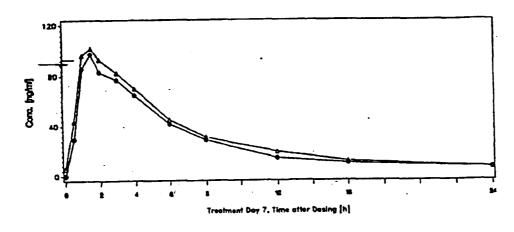
Geometric mean (CV %)

The HCTZ in the two formulations were not bioequivalent. The bioavailability of HCTZ in the combination product is 20 % less than the single entity.

Table 46. Study se866cmb/01: HCTZ Point Estimates (geometric mean) and 90 % CI

1	AUC (ss,t)	Cmax
C vs. B	0.79 (0.58 – 1.08)	0.79 (0.60 – 1.04)

Figure 11. Study se-866 cmb/01: HCTZ Cp (median)



Treatment

Table 47. Study se866cmb/01: HCTZ PK parameters (n=23)

Formulation	B (single)	C (combination)
AUC (ss,t) (ng*h/mL)	686.4 (44 %)	541.8 (91 %)
Cmax (ng/mL)	109.0 (50.0 %)	86.0 (73 %)
Tmax (h)	1.5 (0 -2.0)	1.5 (1.0 – 4.0)

Geometric mean (CV %)

Six subjects were excluded from the PK analysis because concentrations for RNH-6270 and or HCTZ were lower after monotherapy (Treatment A (CS-866) or B (HCTZ)) compared to combination treatment (Treatment C) or vice versa. The sponsor felt that these subjects' concentrations were inconsistent with the other subjects' concentrations.

LOWER AFTER COMBINATION THERAPY

1007 and 1010 - RNH-6270 and HCTZ plasma concentrations and urinary excretion were lower after combination treatment versus monotherapy.

1016 - RNH-6270 plasma concentrations and urinary excretion were lower after combination treatment compared to monotherapy. Plasma concentrations of HCTZ were

also considerably lower after combination treatment compared to monotherapy, but urinary excretion of HCTZ was essentially identical after either treatment.

LOWER AFTER MONOTHERAPY

تتعت

1009 – HCTZ concentrations after monotherapy were below the LOQ and urinary HCTZ excretion was very low.

1022 – RNH-6270 and HCTZ plasma concentration and urinary excretion was lower after monotherapy compared to other subjects and compared to combination treatment.

1023 – RNH-6270 plasma concentrations and urinary excretion were lower after monotherapy compared to other subjects and compared to combination therapy. This subject also had higher plasma concentrations of HCTZ after monotherapy compared to combination therapy. Urinary excretion of HCTZ after monotherapy was low compared to other subjects.

After the sponsor removed the data of six subjects (1007, 1009, 1010, 1016, 1022 and 1023), the RNH-6270 AUC and Cmax PK parameters for the single entity were bioequivalent to that when given together. The same was true for HCTZ. However, rather than a 20 % decrease in bioavailability, there was only a 10 % decrease in bioavailability of HCTZ when given with CS-866 compared to HCTZ alone.

Sponsor's Conclusions: Coadministration of CS-866 with HCTZ had little effect on the pharmacokinetics of RNH-6270. Coadministration resulted in a decrease in the bioavailability of HCTZ of up to 20 %. The sponsor concludes that because of wide intra-subject variability, this decrease in bioavailability is unlikely to be of clinical significance.

Reviewer's Comments: Although the point estimates for RNH-6270 AUC and Cmax were near unity, the confidence intervals were outside of the accepted 90 % confidence interval of 0.80 – 1.25. This is most likely due to the high inter-subject variability. Rather than exclude the six subjects with anomalous concentrations, the sponsor should have accounted for the inter-subject variability and recruited more subjects.

Reviewer's Conclusions: This drug-drug interaction study found that HCTZ does not affect the pharmacokinetics of RNH-6270, however CS-866 decreased the bioavailability of HCTZ-by up to 20 %. There is wide inter-subject variability in the pharmacokinetics of RNH-6270 and HCTZ.

6.3 Dissolution

2000

Volume: 1.29

p. 33 - 74

Procedure: The sponsor tested twelve tablets in each dissolution profile. All—strengths of CS-866/HCTZ film-coated tablets — mg, 20/12.5 mg, 40/12.5 mg, ______ .g and 40/25 mg) manufactured by Sankyo Pharma GmbH were tested. Sampling times were at 10, 20, 30, and 45 minutes. The three media tested were water, JP fluid 1 (pH 1.2) and JP fluid 2 (40.83 g KH2PO4 + 5.6 g NaOH dissolved in 6 L purified water, pH 6.8). The paddle (USP Apparatus II) was used at a speed of 50 rpms.

Due to the hydrolysis of CS-866 to RNH-6270, the dissolution rate of CS-866 was corrected for the amount of RNH-6270 formed during the dissolution test. The amount of RNH-6270 was calculated as a percent of CS-866 and was added to the amount of CS-866. See below for more details.

Dissolution of CS-866

C
V ₀ - Volume of dissolution media [ml] V ₄ - Volume of stock standard solution [ml] D ₁ - Dilution of stock standard solution D ₂ - Dilution of sample

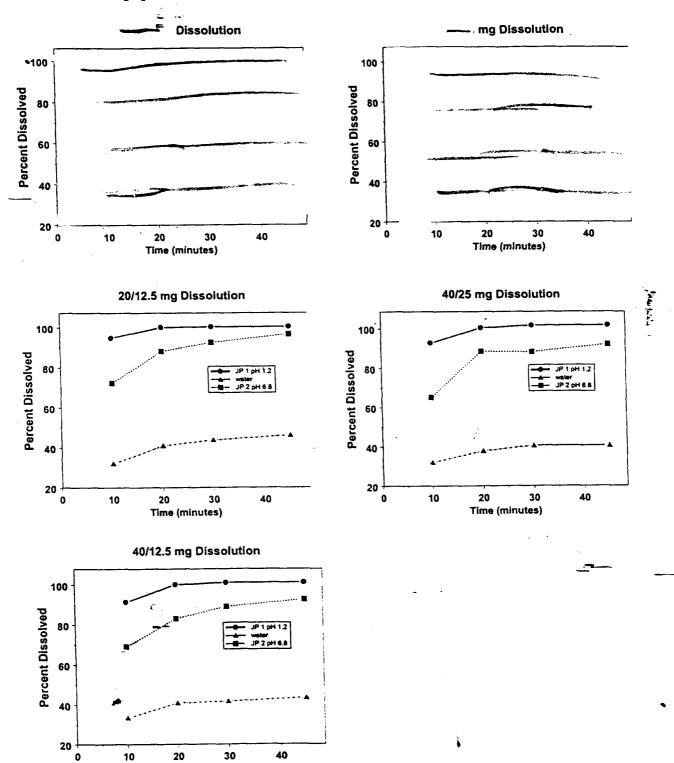
alculation of RNH-6270	C ₁ = Content RNH-6270 [%]	
	w - Weighing CS-866 Standard [m	æl
	F Purity CS-866-Standards [%]	
	F: - Water CS-866-Standards [%]	
	D - Dose of CS-866 in Tablets [m.	2]
	A - Area CS-866 in Sample	
	1 — Area Int STD in Sample	
	A - Area CS-866 in Standard	
	i Area int STD in Standard	
	RRF _{2NKS2} - Relative Response Factor for	
•	RNH-6270*	
€ .	Dil - Dilution Factor 2 for CS-866/h	1C
	mg and 40mg/25mg	

* The RRF for RNH-6270 was determined in the method validation

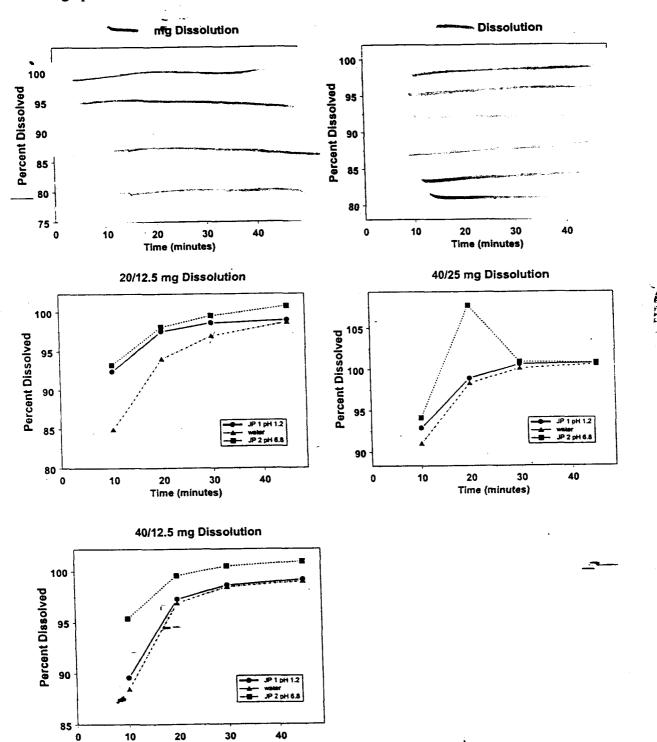
Calculation of CS-866 hydrolysed to RNH-6270

	C ₁ - Cortent RNH-6270 [%] MWcxxxx - Molecular weight of CS-866:
*	
	Mwasusan - Molecular weight of RNH-6270:

Results: The graphs below shows the CS-866 mean dissolution data over time for three media.



Time (minutes)



Time (minutes)

Dissolution Specifications:

The approved dissolution methodology and specifications for Benicar ((olmesartan	medoxomil
are:		

Medium:

1000 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications: Q NLT -, at 30 minutes

The sponsor's proposed dissolution specifications for the combination product are:

Sponsor's Recommended Dissolution Specifications and Methodology for CS-866

20/12.5 mg tablet

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less thar - a. .

40/12.5 mg and 40/25 mg tablet

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than _ at

Sponsor's Recommended Dissolution Specifications and Methodology for HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications:

Q not less than — at

It is noted that the sponsor should not have corrected for the _____ degradation. After review of the stability data (see CMC review), it was decided that the sponsor may not meet the specifications Q= at A product with a release of only is less likely to meet bioequivalence than a product with a release of 100 %. Since a higher specification is better, the following is recommended for the combination product:

CS-866

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50**...pm**

Specifications: Q NLT -

HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications: Q NLT - at -

Waiver Request:

The sponsor demonstrated bioequivalence (BE) between the to-be-marketed formulation tablet of 20/12.5 mg and the single entities (study 866-126). The sponsor is requesting a waiver from doing the human BE study for the 40/25 mg tablet. The following data support the waiver:

• The pharmacokinetics of both drugs are linear over the dosage range.

• The dissolution profiles of the reference (20/12.5 mg tablet) and test product (40/25 mg tablet) are similar. The reviewer's calculated similarity factors (f2) for CSS-866 are between 50-100 (see table below).

Table 48. Similarity factor (f2) for CSS-866 20/12.5 mg and 40/25 mg

	Medium	f2
-	Water	75.4
	pH 6.8	75.4

• The f2 was not calculated for CSS-866, pH — and for HCTZ because dissolution was greater than —, by

• The 40/12.5 mg tablet (reference) is proportionately similar to the 40/25 mg tablet (see table below). The difference in HCTZ is accounted for in the lactose.

Table 4.3. 1: Quantitative formulation of the Sankyo Pharma GmbH CS-866HCTZ

Ingredient	tablet	20/12.5 mg tablet	40/12.5 mg tablet	tablet	40/25 mg tablet
CS 8661		20 mg	40 me		40 mg
Hydrochlorothiazide		12.5 mg	12.5 mg	_	25 mg
vlicrocrystalline cellulose					
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Hydroxypropyl cellulose	The control of th				
Hydroxypropyl cellulose Magnesium Stearate		Control of the Contro			
Hydroxypropyl cellulose Magnesium Stearate Tablet Core Weight	Round	Round			Oval 4 15 x 7 mn

Reviewer's Conclusions:

A biowaiver can be granted for the 40/25 mg tablet.

Dissolution Specifications:

The following dissolution specifications are recommended:

CS-866

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed: 50 rpm
Specifications: Q NLT at 45 minutes

• HCTZ

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Specifications: Q NLT — at 15 minutes

APPEARS THIS WAY ON ORIGINAL

6.3.1 Individual dissolution data

The individual dissolution data for CS-866 are shown in the pages that follow.

ing CS-866 / HCTZ tablet

lot 3138v01006

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

Sample		% CS-866	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
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lot 3138v01006

Medium:

900 mL, <u>purified water</u>, 37°C USP II (paddle)

Apparatus:

Speed:

50 rpm

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	10 minutes	10 minutes 20 minutes	

* = Missed sample, no data

• lot 3138v01006 Medium: Apparatus: Speed:

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle) 50 rpm

Sample		% CS-866	Dissolved	
защие	10 minutes	20 minutes	30 minutes	45 minutes
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lot 3148v01002

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

• Apparatus:

USP II (paddle)

Speed:

50 rpm

Sample		% CS-866	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
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Mean			All the second s	Carried State Control of the Control
Std. Deviation				

lot 3148v01002

Medium:

900 mL, purified water, 37°C

Apparatus:

USP II (paddle)

Speed:

Sample		% CS-866	Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes		
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lot 3148v01002 Medium: Apparatus: Speed:

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle)

Sample	% CS-866 Dissolved	
	10 minutes 20 minutes 30 minutes 45 minutes	•
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lot 3139v01004

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

• Apparatus:

USP II (paddle)

Speed:

-

50 rpm

Sample		% CS-866	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1 2	الراسية المحاض	والمائية والمراجع فالمستعمل والمنافية والمنافية والمنافية والمنافية والمنافية والمنافية والمنافية والمنافية والمنافية	というない 大山田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田田	
3		Market Continues and springers of States and American States and American		A CONTRACTOR OF THE PROPERTY O
4	And the second second	and the second s	A SERVICE CONTRACTOR C	
		And the state of t	and the state of t	en energy sight services and a service
7	un en	en 1950 iste i della serggidda ethe delesidayen i et i i i delesidagen i estilla i		A STATE OF THE STA
	t in the second	ر موجود میشود که او در میشود در در در در در میشود در میشود در میشود در در میشود در میشود در میشود در میشود در م	and a supplementary of the state of the stat	and the second of the second o
10	The second	gggt a filippakthilare to go control or suggest of the file		guales de la minima estada estada Balancia estada est
11		man in the state of the state o		
Mean	94.79	100.02	100.35	100.42
Std. Deviation	1.71	0.91	0.92	1.02

lot 3139v01004

Medium:

900 mL, purified water, 37°C USP II (paddle)

Apparatus: Speed:

Sample		% CS-866	Dissolved /	
	10 minutes	20 minutes	30 minutes	45 minutes
$\frac{2}{3}$				
3 4				
$\frac{7}{5}$				
6	~~~	rita bar makalagan yi risi sering sabah dahara ik ya sabah <u>da pangan da sabah da</u>	d & you couldn't have a section of the section of t	
7]	· ·		· · · · · · · · · · · · · · · · · · ·	
8	, nyse yanyeni	the state of the s	gyper Zamielick i server en og det omstå her det med en	The state of the s
- 10	ga - per els		Beautiful for a regulate a difference commencement and accom-	and the state of t
11.	and the same of th	arting Chapter (1992) Palabatia (Ig. 1985) Salabatian and Salabatian (Ig. 1985) Salabatian and Salabatian (Ig.	The state of the s	og
-12	* ··=··	The second of th	The second secon	
Mean	32.05	40.96		46.0
Std. Deviation	2.08	0.90	0.76	1.28

lot 3139v01004

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle)
50 rpm

Medium:
Apparatus:
Speed:

Sample		% CS-866 E)issolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1			The state of the s	المعادية المستحدد المستحدد المستحدد المستحدد المستحدد المستحد المستحدد المس
2	. o Library	The second secon	CONTRACTOR AND CONTRACTOR OF THE PROPERTY OF T	one of William or Salar Windowski, and or
3		kanan kanan kanan sakalah sami maka dan sakan saka saka saka saka saka saka s	Markey	
4	, Alas Santa	Community and the second section of the sect	· Transitation of the material and the second	
5	_	ge i transporte i la constitución de la contraction de la contract		6 H
		retraining		
7		and the control of th	and a second resident designation and the second and the second and the second	* **
. 8	_ unanapaga	والمعارض المتعارض المتعارض والمتعارض	ter and the analysis of the second second	e Carl
9	<u>)</u>	پېژېون سېښې د د د د د د د د د د د د د د د د د د	gannagan gan district of the second section of the section of the second section of the	
10		ينقلاه والمتحافظ والمتحافظ والمتحافظ والمتحافظ والمتحافظ	erentago o la la companya de la	-
11		Surregues and a second of the	and the second s	
12				
Mear		88.04	92.51	96.
Std. Deviation	n 2.93	1.43	1.26	1.0

lot 3149v01002

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C USP II (paddle)

Apparatus: Speed:

50 rpm

Sample		% CS-866 I	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1			AND ADDRESS OF THE PARTY OF THE	
2		" PARTITUM MARINEM VICTOR AND		
3		and the second of the second o		and the second of the second o
4	The state of the s	a pala a la ser a la participa de la participa		
5	• Salah Sala	Section and the section of the secti	Consider the Control of the Control	The second secon
()		magaille and the second of the	The second secon	grante i sua significante e contra como esta e contra contra e contra co
<u> </u>			The second secon	
9		the management of the second		
10	n programmer		* *** ***	
] [A CONTRACTOR OF THE CONTRACTOR	Same of the control of the same of the sam	
12				
Mean	92.65		101.71	101.7
Std. Deviation	3.61	1.33	1.08	1.3

lot 3149v01002

Medium:

900 mL, purified water, 37°C

Apparatus: Speed:

USP II (paddle)

Sample		% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes	
1				Marie Conservation and section .	
2 1			e din primer :		
3					
4			The second of th		
5	i y www.				
6		g verta v	and the second state of the second se	esp.	
7					
_8				The state of the s	
9			CONTRACTOR		
10	· Andrewson and the second sec	The second secon	en e	The Estate of the Control of the Con	
11	yanga Cantaling ang ang ang ang ang ang	Contract to the second to the	anan kanan 1920-ya saka da kanan erene ili. Anan kanan ka		
12	*19 - 10				
Mean	32.04	37.76	40.49	40.	
Std. Deviation	1.49	1.05	0.88	0.	

lot 3149v01002 Medium:

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle)
50 rpm

Apparatus:
Speed:

Sample		% CS-866	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
ı				
2				
3	- Commercial Services			AND THE REAL PROPERTY AND THE PARTY AND THE
4	1_		to the control of the	
6				
- 8	_		్ అంటుత్తు. ముంచు ముహిక్ కి.మీ. కొనిసిన కేశం పోతోకోగా	
. 9		and the state of t	a secure segmentarios de la companya del companya della companya d	and the second s
10			a remarks of the second	The second secon
11	- Antique a		ر المار در المار الم المار المار ال	
12	* .	The second section of the second section secti	maganin ya Basangaran ili kuta da asara	Commence of the Commence of th
Mean	65.06	88.38		91.9
Std. Deviation	3.07	15:41	0.77	1.1

lot 3140v01005

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C USP II (paddle)

Apparatus: Speed:

50 rpm

Sample		% CS-866 D)issolved	
	10 minutes	20 minutes	30 minutes	45 minutes
l				
2				
3				
4	<u> </u>			
5		The state of the s		
6	- An extraordinate special spe	The second secon	Same and the second of the sec	
7		والمعارض المساوية والمقاول فالإفارات الإنجاب والموارد والمساورة والمعارض والمساورة والمقاولة والمقاولة والمساورة والمساورة والمعارض والمساورة والم	The state of the s	
8				
. 9		Marrier resident distinguis de l'estate de la company de l'estate de la company de l'estate de la company de l	The same and the same processing and an advantage of the same and the	
10		erindet san Satur om Metallerann, vag god, i Trifa o den in stagegen gele eine einer in som Friedrich. Den sam eine einer einer einer einer eine einer eine eine		And the state of t
11	C.C. Called Street, Co.	大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大大		
12				
Mear		100.20	101.13	101.3
Std. Deviation	3.73	1.17	1.21	1.1

lot 3140v01005

Medium:

900 mL, purified water, 37°C USP II (paddle)

Apparatus: Speed:

Sample		% CS-866	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
2	~			
3				The state of the s
4	S. A. S.	The same of the sa		
5	· provident description	AND THE PROPERTY OF THE PARTY O		
6	- · · · · · · · · · · · · · · · · · · ·	The second section of the second section of the second section is a second section of the second section of the second section is a second section of the section of t	The same of the sa	
7			First righter of the second stay in the second stay of the second stay	
8		a the second		
y	Problem of the Pro- En		minimaka seperaga, masahirang communistration di seperat	The state of the s
10	Supply when the con-	The second secon	The second secon	The party of the p
11	الله الله الله الله الله الله الله الله	and the second of the second o	and the state of t	AND THE PROPERTY AND ADDRESS OF THE PARTY OF
12	" manife to the			
Mean	33.55	40.93	41.68	43.
Std. Deviation	1.58	1.35	0.73	1.

lot 3140v01005 Medium: Apparatus: Speed:

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle)
50 rpm

opeca.	20.P							
Samp	le	% CS-866 Dissolved						
		10 minutes	20 minutes	30 minutes	45 minutes			
	11				Marie Marie Marie La Marie Mar			
<u> </u>	2							
	3	er all ander	چەرى بەرسى بىيە ، مرەكسىلىنىچ		The second secon			
	4	· The state of the			Ballitin			
	5	. •	and the second s	The second secon	A Company of the Comp			
·	6	The second	and the second s	The state of the s	Comments of the Comments of th			
	7			The Manager of the Control of the Co				
	. 8	-	and the second representation of the second	1				
	9		. ••••	in the second se	2000			
	10			The same of the sa	n.m.,			
	11	. * * *	a compress Promises, a	The processing of the second o	and the second second second			
	12	- %	Lamon y 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	And the second of the second o				
	Mean	69.14	83.12	89.21	92.68			
Std. I	Deviation	2.86	1:10	1.18	0.78			

The individual dissolution data for HCTZ are shown in the pages that follow.

mg CS-86 / HCTZ tablet

• lot 3138v01006

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

Apparatus:

USP II (paddle)

Speed:

50 rpm

% HCTZ Dissolved 10 minutes 20 minutes 30 minutes 45 minutes			
5 minutes			
Andreas de la companya de la company			
· · · · · · · · · · · · · · · · · · ·			
and the same of th			
CONTRACTOR OF THE PARTY.			

lot 3138v01006

Medium:

900 mL, purified water, 37°C

Apparatus:

USP II (paddle)

Speed:

Sample		% HCTZ	Dissolved		
	10 minutes	20 minutes	30 minutes	45 minutes	
1			englarente et engletsellenske (se g. e. a.). voor, de kooste promier to glekke begegen de ge		
2	* Same	大田の東京の東京の大田の大田の大田の大田の大田の大田の大田の大田の大田の大田の大田の大田の大田の			
3	_	・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・			
4	·		-		
5					
6	_				
7					
8 -	ne _{a co} n established				
9	Contraction of the second	الله الله الله الله الله الله الله الله		2000	
	Tana ana		· · · · · · · · · · · · · · · · · · ·		
10		A STATE OF THE PARTY OF THE PAR			
10 11	n or and the	· · · · · · · · · · · · · · · · · · ·		and the second s	
10 11 12	n or and the	· · · · · · · · · · · · · · · · · · ·		and the second s	
10 11 12 Mean	n or and the	· · · · · · · · · · · · · · · · · · ·		and the second s	

lot 3138v01006

Medium:

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle) 50 rpm

Apparatus:
Speed:

Sample		% HCTZ	Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes		
1						
2				THE PARTY CONTROL OF THE PROPERTY OF THE PARTY OF THE PAR		
3						
4		CONTRACTOR AND ADDRESS OF THE PARTY OF THE P	C AND COMPANY OF THE PROPERTY			
	では、大きなないというできないというできないというできない。 またい はいまま はいかい はいまま はいかい はいまま はいまま はいまま かっぱい はいまま しゅうかん しゅう					
6	19 Street of the profession of the contract of					
7	societate	And the second section is a second second section in the second section is a second second section in the second section is a second second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section in the section is a section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in th	The second secon	COMPLETED CONSIDER		
- 8	ligh way	теажен. Сосинальный общений на г	the latter than the second of	And the second section of the section o		
9	* □43534**	er despetajo de terreto mos este esta esta la esta esta esta esta esta esta esta est	garanteen en	aller principal and a second s		
10		range a range or have of the property with the last limited the	a history of the first the second was seen to be a second of the second	- Color 125-		
11		The second of th	THE STATE OF THE PARTY OF THE P	5.5		
12			en in water grandstaten in the grant with			
Mean			ar en			
Std. Deviation		n vina na serie martini nakatin kakata	NOTE: THE STATE OF	. 4.		

lot 3148v01002

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

• Apparatus: Speed:

USP II (paddle)

50 rpm

Sample		% HCTZ	Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes		
	_			The state of the s		
2	_		magnyaya, na ana in 1984 an in			
3 [Mariana de 1771	The second section of the sect	Progenition with the second control of the s	Markets of constitution of Parket Constitution (1997)		
4	neste e e e	Secretary and the Control of the control of the secretary control of the control				
5		and the second of the second of the second of the second	A CONTRACTOR OF THE PROPERTY O			
6	Margar 1.	er en leer bestellt	para di santa di san			
7			energy and a state of the second			
. 8			والمهار والمعارفة والمهار والمناز والمناز والمناز والمناز والماران			
9		of comment company, see	na managana (na gangganggan) na managangganggangganggang na managangganggangganggangganggangganggang	Marketon and State Control of the Co		
10	F 1 4	and the second s	en a de la composition della c			
11	~	Committee of the second section of the section of the second section of the second section of the second section of the section of the second section of the	ない 強ない こうと はい おおける 真にまする 事であるない 選集	Carried States of the Control of the		
12		Committee of the second section of the section of the second section of the secti	time to you have to be the commentation of the same of	The second section of the second section is a second section of the second section is a second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a section in the second section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section in the section is a section in the section in the section in the section is a section in the section is a section in the section in the section in the section is a section in the section in		
Mean	-	A STATE OF THE PARTY OF THE PAR				
Std. Deviation	~	and the same	· · · · · · · · · · · · · · · · · · ·	Marie Company of the		

lot 3148v01002

Medium:

900 mL, purified water, 37°C USP II (paddle)

Apparatus: Speed:

Sample		% HCTZ	Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes		
1						
2	g. , 1949 agrangia distrib ti					
3	ه المنظمة الماريخ	مترضيط بيستان والمستهدين والمسيد والمستهدية والمتعددة وا				
6						
	Telepopus of the	Canada a Lagra James de Pere de 1990 d	adamente de la composição de la composição Composição de la composição de	The state of the s		
8			ander mellen som en			
						
			in the state of th			
		الله المستويدي المستو ولا المستويدي المستو	enganisas (n. 1916)			
12		and the second s	Market State of the control of the state of the control of the state o	- Committee of the comm		
Mear	<u>'</u>	The second secon	and the second of the second s	California programme and the second		
Std. Deviation	n					

lot 3148v01002

900 mL, JP fluid 2, pH 6.8, 37°C

Medium:
Apparatus:
Speed:

USP II (paddle)

Sample		% HCTZ	Dissolved			
<u> </u>	10 minutes	20 minutes	30 minutes	45 minutes		
1			and the second s	Marie Committee and the second sections		
2		The second section of the section of th				
3		The second secon				
4	an angeneral	A Section of the Control of the Cont				
	The state of the s					
- 6		and the second of the second o				
		and the second of the second of the second				
. 8		and the second s	ally flavor in against the second	No. of the second secon		
10	B .					
10	+	gradient state of the state of	park	š. **		
12	†	A STATE OF STATE OF	and the second second	1191		
Mean	 					
Std. Deviation	├	- And the Control of				

lot 3139v01004

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

• Apparatus: Speed:

USP II (paddle)

50 rpm

Sample		% HCTZ D	issolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1			and the second second second second second	CONTRACTOR STATEMENT OF THE STATEMENT OF
2	4 The Section	manufacture of the second second	The state of the s	Brown Strawer or .
3	and the second s	A Section 1997	and the second s	ar e
4	• ••• • ;	3 m mark 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	the make the first of program is a meaning type of	
5	الاجتماع ا	C 4 5 M	The second second second	
- 6		La Contrata Marie Carlos Contrata Contrata Contrata Contrata Contrata Contrata Contrata Contrata Contrata Contra		
7	-	Contract to the second	ty yezh a ar yezhoù e savezhoù a ar e	to the contract of the contrac
8		الاراقة ما المقايد المهاري المهار	a dos.	-4
. 9	-	\$ A Company of the	Andrew Control	with the second
10	4 1 §≥ t •••	Para di La Cara di Salamana di	· · · · · · · · · · · · · · · · · · ·	and the entrance
11	 	ه او در محمول ارب در در در در و المعالمين في المعالمين و المعالمين المعالمين و المعالمين المعالمين و	the parties of the second state of the second state of the second	
12	- t -	The second secon	Signature and the second	*
Mean	92.41	97.52	98.60	98.9:
Std. Deviation	2.72	1.93	1.29	1.04

lot 3139v01004

Medium:

900 mL, purified water, 37°C

Apparatus:

USP II (paddle)

Speed:

Sample		% HCTZ D	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1			大学 はない かんかん これのない ないかん かんかん かんかん かんかん かんかん かんかん かんかん かん	w/) %
2	THE PROPERTY OF THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TWO IS NAMED IN COLUMN T			The state of the s
3	No constitution of	A Company of the Comp		
4	- Carrier to	was in	40 Jan 1997 - 1998 - 1997 - 1997	· * .5
5	<u>.</u>	The second secon	Continue of the Continue of th	The state of the s
6	et set times	e i de la complete de company de la Riberta de la completa del completa de la completa de la completa del completa de la completa del la completa de la completa del la completa de la com	The second secon	n suspen
7 8	-		gantan - domina de la callanta de la callan	والتي المستر برسيهيوا المعينوا
8	• · · ·	The second secon	ود مداهاتهم موار از ۱۳۰۰ ما ۱۳۳۰ ما ۱۳۳۰	ngamen against say
10	-	and the second	er i korresto de esperado de esperado en el el el	Manager and the control of the contr
11	<u>-</u>	And the second of the second o		
12	-			
Mean	84.93	94.01	96.93	98.6
Std. Deviation	6.08	2.85	2.10	1.5

lot 3139v01004 Medium: Apparatus: Speed:

900 mL, JP fluid 2, pH 6.8, 37°C

USP II (paddle)

Sample		% HCTZ I	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1				AND THE PROPERTY OF THE PARTY O
2	ig a seed a reason and a supply of the seed of the see	and the state of t	and the state of t	NATO WARE THE MEDITE TO THE MEDITE TO THE
4	- For Hardway Lance	and the second section of the sectio	कंपनिवर्तः १९७४-४८ क्षण्यक्षेत्रकेविक्वयस्य स्थापनः । १८८८ १८ । अन्य १८८४ व्यक्तिः । अस्य १८८४ । अस्य १८८४ वर्	
5	i po de especialista.	on the contraction of the second seco	and the state of t	error and an artist of the second
7		and the state of t	The state of the s	and the second s
. 8	<u>]</u>	the second second second second	produced services of the consequences.	•
9		and the second of the second o	en e	-
10	and the second s	A - A Company of the second se	Communication of the Communica	The second of th
11	-	S	ولا المنازين والماستون والماسور	ti i i i i i i i i i i i i i i i i i i
Mean		98.08	99.53	100.7
Std. Deviation		2.21	1.59	1.2

lot 3149v01002

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

• Apparatus: Speed:

USP II (paddle)

50 rpm

Sample		% HCTZ D	issolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1				-
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12	→ Wenda			
Mean	92.86	98.89	100.61	100.74
Std. Deviation	3.11	1:44	1.21	1.48

lot 3149v01002

Medium:

900 mL, purified water, 37°C USP II (paddle)

Apparatus:

Speed:

Sample		% HCTZ D	issolved	
	10 minutes	20 minutes	30 minutes	45 minutes
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12	•			
Mean	90,99	98.30	100.10	100.55
Std. Deviation	3.17	1.73	1.31	1.30

lot 3149v01002 Medium: • Apparatus: Speed:

900 mL, JP fluid 2, pH 6.8, 37°C USP II (paddle) 50 rpm

Sample		% HCTZ	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
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Mean	94.11	107.70		100,76
Std. Deviation	3.85	19.04	0.60	1.16

lot 3140v01005

Medium:

900 mL, JP fluid 1, pH 1.2, 37°C

• Apparatus: Speed:

USP II (paddle)

50 rpm

Sample		% HCTZ I	Dissolved	
	10 minutes	20 minutes	30 minutes	45 minutes
1				Britania - Harris Maria - Landardo - Landard
2	er en de descrier en	and the complete and th		
4				
5	1	12 *** *** *** *** *** *** *** *** *** *	The second of th	
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9	+	er en		LE ANNO METERS
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12				
Mean	89.57	97.26	98.63	99.1:
Std. Deviation	3.68	1.79	1.50	1.2

lot 3140v01005

Medium:

900 mL, purified water, 37°C USP II (paddle)

Apparatus:

Speed:

Sample		% HCTZ D	issolved	
	10 minutes	20 minutes	30 minutes	45 minutes
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10	A TOTAL PORT	· · · · · · · · · · · · · · · · · · ·	The second secon	and the last think in the second of
١T١	•	and the second s	1 Transaction	
12			33.45.1	
Mean	88.45	96.89	98.45	98.98
Std. Deviation	2.40	1.54	1.30	1.1

lot 3140v01005 Medium: • Apparatus: Speed:

900 mL, JP fluid 2, pH 6.8, 37°C

USP II (paddle)

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
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12	Ī			
Mean	95.37	99.58	100.49	[00]
Std. Deviation	3.23	1.28	1.13	1

6.4 Batches used in pharmacokinetic studies and 866-318 (pivotal study)

Table 49. Batch numbers for to-be-marketed combination tablet

Strength Lot no.	3138V01006	20/12.5 mg 3139V01004	3140V01005
Clinical study		866-126	
•	866-127	866-127	866-127

Table 50. Batch numbers for 10 mg CS-866 tablet

Lot no.	B99T19
Clinical study	866-318

Table_51-Batch numbers for 20 mg CS-866 tablet

Lot no.	B99T20	2234v99001
Clinical study	866-126	Se-866cmb01
	866-318	

Table 52. Batch numbers for 12.5 mg HCTZ capsule

Lot no.	015103
Clinical study	866-126
•	866-134

Table 53. Batch numbers for 12.5 mg HCTZ over-encapsulated to-be-marketed capsule

Lot no.	1006138/02
Clinical study	866-134

Table 54. Batch numbers for 12.5 mg HCTZ tablet

Lot no.	2145601
Clinical study	866-126

Table 55. Batch numbers for 25 mg HCTZ tablet (HCTZ

Lot no.	7080275t
Clinical study	Se-866cmb01

6.5 Formulations used in the studies

TABLE 6.5.7.1a: Formulations Used in CS-866HCTZ Clinical Trials

Process No/Change	Strength (mg)	CS-866HCTZ Dosage Form:	Study No.	Lot. No.	Tablet Batch Size	# Manufacturer
A	7	Tablet	866-127	3138V01006		Sankyo Pharma GmbH
A	1 20/12.5	Tablet	866-126. 866-127	3139Y01004		Sankyo Pharma GmbH
A	40/12.5	Tablet	866-127	3140V01005		Sankyo Pharma GmbH

CS-866 HCTZ combination tablet
A Commercial process

TABLE 6.5.7.1b: Formulations Used in CS-866 Tablets in Combination with HCTZ Preparations in Clinical Trials

Process No/Change	Strength (mg)	CS-866* Dosage Form	Study Na.	Lot, No. ⁴	Tablet / Capsule Butch Size	Manufacturer
		Tablet	SE-88-6:19	224 2235/V95021		ankyo Co., List
	Placebo	Tablet	SE-86-6/17	225 2235 V95022		Sankyo Co., Ltd. 🔑
		Tablet /	SE-86-6-19	226 2235V95023		Sanicyo Co., Ltd.
		Tablet	SE-896/10	296 2235 V 97001		Sankyo Co., Ukl.
	\	Tablet	Nov-305, 856-306	295		Sankyo Co., Usa.
		Tablet	SE-866/10a)1	2235V98001		- Sankyo Phamsa CimbH
		Tablet	N66-318	B99 F22		Sankyo Co., Ltd.
		Tablet	St. 866/19	D97 104 2235 V97003		Sankyo Co., Ltd.
	1	Capsale	N66-318	100690-02/5		A SHARMAN
		Capsa le	864-313	100690-07/5		
	1	Capsale	846-419	1(0)698-01		
A. B	2.5	Tablet	866-305	290	-	Sankyo Co., Ltd.
A. B		Tablet	866-305, 866-306, SE-866/10	291 2232V97001		Sankyo Co., Ltd.
B. C. D	- 5	Tablet	SE-866/10-01	2232V98014		Sankyo Pharma GmbH
A. B	1	Tablet	SE-866/10, SE-866/19	D97T01 2232V97003		Sankyo Co., Ltd.
A, B		Tablet	866-305, 866-306, SE-866/10, SE-866/17, SE-866/19	292 2233 Y9700 1		Sankyo Co., Ltd.
B, C, D	10	Tablet	SE-866/10-01	2233V98016		Sankyo-Phoema GmbH
A.B	–	Tablet	SE-866/19	D97T02 2233V97003		Sankyo Co., Ltd.
A, B		Tablet	866-318	B99T19		Sankyo Co., Ltd.

TABLE 6.5.7.1b: Formulations Used in CS-866 Tablets in Combination with HCTZ Preparations in Clinical Trials (Continued)

roceи No/Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.	Tablet Batch Size	Manufacturer
r B		Tablet	866-108, 866-305,	293		sankyo Co., Ltd.
	20		866-306, SE-866/10, SE-866/17	2234\97001		•
3, C, D	┩¯	Tablet	SE-866/10-01	2234Y98013		Sankyo Pharma GmbH.
A. B	1	Tablet	SE-866/19	D97T03 2234V97009		Sankyo Co., Ltd.
D	┪	Toblet	SE-866CMB/01	2214V9900I		Sankyo Pharma GmbH
L. B		Tablet	866-126, 866-318	B99T20		Sankyo Co., Ltd.
N. B	⊣	Tablet	866-321	E99T03		Sunkyo Co., Etd.
L B	┥	Tablet	866-419	B00T17		Sankyo Co., Ltd.
A. B -	140	Tablet	866-305, 866-306	294		Sankyo Co., Ltd.
A. B	- `	Tablet	866-318	B99T21		Sankyo Co., Ltd.
A. B	┥	Tablet	866-419	E99T06		Sankvo Co., Ltd.
VA.	20	Suspension	\$66-108	K97T05		Sankyo Co., Ltd.
NA	16	RNH-6270 solution	866-108	K97T01		Sankyo Co., Ltd.

*Except as noted A =

TABLE 6.5.7.1c: Formulations Used in CS-866 Tablets in Combination with HCTZ Preparations in Clinical Trials

Strength (mg)	HCTZ Dosage Form	Study No.	Lot. No.	Tablet/Capsule Batch Size	Manufacturer
Placebo	Capsulc	866-318	100690-02/5 100690-07/5		-5y 2300-400/
	Capsule	866-419	100698-01		
	Tablet	866-126	2145601	Commercial	
	Capsule	866-126	015103	Commercial	
	Capsule	866-134	015103	Commercial	
	Capsule	866-134	015103 106138/02		
	Capsule	866-305	706602	Commercial	
12.5	Capsule	866-306	706602	Commercial	A STATE OF THE STATE OF
	Capsule	866-318	006901 100690-08/5		_
	Capsule	866-321	012301	Commercial	
	Capsule	866-419	010801	Commercial	Name of the last o
	Tablet	SE-866/19	2000201	Commercial	THE REAL PROPERTY.
5	Tablet	866-419	K5406	Commercial	1100
	Tablet	SE-866CMB/01	7080275T	Commercial	
	Tablet	SE-866/10, SE-866/10-01	203890	Commercial	
	Tablet	SE-866/10 SE-866/10-01	203900	Commercia	
	Tablet	SE-866/17	7080275	Commercia	
	Tablet	SE-866/19	2000502	Commercia	1

^{*}Study 866-134 did not include the use of CS-866 tablets. This was a bioequivalence study of market-image versus overencapsulated market-image

B =

C = D=

NA= Not Applicable
If more than one Lot No, is indicated the first Lot No, is the one assigned by the manufacturing site; the second Lot No, is the one subsequently assigned by the

hydrochlorothinzide capsules.

If more than one Lot No, is inclicated the first Lot No, is the one assigned by the manufacturer the second Lot No, is the lot number assigned by the - during overencepsulation with capsale.

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/s/

Nhi Nguyen 4/10/03 03:04:05 PM BIOPHARMACEUTICS

Patrick Marroum 4/10/03 03:23:09 PM BIOPHARMACEUTICS